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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,200	04/03/2001	Douglas A. Russell	18337.006	5401

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ARNOLD & PORTER
Attn: IP Docketing Department Room 1126B
555 - 12th Street NW
Washington, DC 20004-1206

EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 01/13/2003 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/824,200	Applicant(s) RUSSELL ET AL.	
	Examiner Jeffrey Fredman	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13,20,22 and 91-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13,20,22 and 91-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's cancellation of the nonelected claims is acknowledged.

Specification

2. The objection to the disclosure is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

2. Claims 1-7, 9, 10, 13, 20 and 91-93 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (U.S. Patent 6,020,169).

Lee teaches a method for producing a cytokine, such as IL-4, which is free from amino acid modifications or novel glycosylation (see figure 13 which shows that IL-4 has same molecular weight as recombinant human IL-4) in a plant host system wherein said plant host system has been transformed with a chimeric nucleic acid sequence encoding said cytokine (see column 6, lines 6-21 and column 20, lines 15-67) comprising the steps:

(a) cultivating said transformed plant host system under the appropriate conditions to result in the expression of said cytokine in said plant host system (see column 20, lines 15-67)

(b) wherein said cytokine accumulates to a level greater than 1% of the total soluble protein in a sample of said plant host system (see figure 11, where clone 81 produced over 1000 ng of IL-4 per g Calli, which inherently represents more than 1% of the total soluble protein). Lee also expressly teaches that expression of over 1% of total protein is achievable (see column 1, line 45).

Lee purifies the cytokine using SDS-PAGE and TCA precipitation (see column 21, lines 7-16).

Lee teaches a chimeric nucleic acid molecule which comprises the cloned plant cytokine gene (see column 9, lines 58-60) under the control of a plant promoter sequence (see column 9, line 60 to column 10, line 2) as well as signal sequences including signal sequences to the endoplasmic reticulum (see column 5, line 51 to column 6, line 5).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (U.S. Patent 6,020,169) as applied to claims 1-7, 9, 10, 13, 20, 91 and 92 above, in view of Boone et al (U.S. Patent 5,849,883).

Lee teaches a method for producing a cytokine, such as IL-4, which is free from amino acid modifications or novel glycosylation (see figure 13 which shows that IL-4 has same molecular weight as recombinant human IL-4) in a plant host system wherein said plant host system has been transformed with a chimeric nucleic acid sequence encoding said cytokine (see column 6, lines 6-21 and column 20, lines 15-67) comprising the steps:

(a) cultivating said transformed plant host system under the appropriate conditions to result in the expression of said cytokine in said plant host system (see column 20, lines 15-67)

(b) wherein said cytokine accumulates to a level greater than 1% of the total soluble protein in a sample of said plant host system (see figure 11, where clone 81 produced over 1000 ng of IL-4 per g Calli, which inherently represents more than 1% of

the total soluble protein). Lee also expressly teaches that expression of over 1% of total protein is achievable (see column 1, line 45).

Lee purifies the cytokine using SDS-PAGE and TCA precipitation (see column 21, lines 7-16).

Lee teaches a chimeric nucleic acid molecule which comprises the cloned plant cytokine gene (see column 9, lines 58-60) under the control of a plant promoter sequence (see column 9, line 60 to column 10, line 2) as well as signal sequences including signal sequences to the endoplasmic reticulum (see column 5, line 51 to column 6, line 5).

While Lee teaches expression of GM-CSF (see column 22, example 4), Lee does not expressly teach expression of G-CSF in plants.

Boone suggests expression of G-CSF in plants (see column 10, line 9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to express G-CSF in plants using the method of Lee since Boone expressly teaches that the G-CSF polypeptides can be the product of "prokaryotic or eukaryotic host expression (e.g. by bacterial, yeast, higher plant, insect and mammalian cells in culture)(see column 10, lines 6-9)". An ordinary practitioner, taught by Lee a method which teaches "high-level gene expression (abstract)" in plants would have been motivated to apply this high level gene expression method to express the G-CSF of Boone since Boone expressly suggests plant cell expression of the protein. Further an ordinary practitioner would have been motivated in order to get more protein, since Lee teaches high level expression.

6. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (U.S. Patent 6,020,169) in view of Schouten et al (FEBS Lett. (1997) 415:235-241).

Lee teaches the limitations of claims 1-7, 9, 10, 13, 20, 91 and 92 as discussed above. Lee teaches signal sequences for ER expression (see columns 5 and 6) but Lee does not teach the use of KDEL sequence at the 3' end of the sequence.

Schouten teaches the use of a KDEL sequence at the 3' end of proteins for ER expression (see abstract, page 235, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the KDEL sequence of Schouten in the cytokine expression method of Lee since Schouten states "It was unexpectedly shown that addition at the C-terminus of the ER retention signal KDEL resulted in significantly improved expression levels (abstract)". An ordinary practitioner would have been motivated to use the KDEL retention signal of Schouten in the expression method of Lee in order to achieve significantly improved expression levels, since more protein is the desired result by any ordinary practitioner.

Response to Arguments

7. Applicant's arguments filed December 6, 2002 have been fully considered but they are not persuasive.

Applicant argues that the prior art Lee reference does not show production of 1% of soluble protein and that there is no technical reasoning or scientific fact supporting this inherency in Lee. Lee shows that 1% of Total protein is the newly expressed cytokine. The insoluble proteins in cells are composed of the cells own nuclear matrix

proteins such as laminin along with microtubule proteins and other structural elements. Since the exogenous proteins expressed by Lee are not structural elements of the cells in which they are expressed, they would not be associated with the insoluble fraction. Soluble protein is a fraction of total protein and since cytokines are known to be soluble proteins which operate by traversing the bloodstream, an ordinary scientist would expect that if, for example, only ½ of the cellular protein is soluble, then if Lee shows the cytokine makes up 1% of Total protein, it would make up twice as much of the small subset of soluble protein or 2% of that compartment. The requirement of an inherency argument is that , as MPEP 2112 notes "the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Here, 1% of total exogenous protein in a cell, including a leaf cell, necessarily implies that at least, and probably more than 1% of that protein will be soluble, since the set of soluble proteins is a subset of total protein. So 1% of the larger set necessarily implies more than 1% of the smaller subset of soluble proteins.

Applicant then argues that the western blot is insufficient evidence to show that the protein is free from amino acid modification or glycosylation. This argument is simply incorrect. The burden of proof for the prima facie case is to show that, more likely than not, the protein is free from amino acid modification or glycosylation. Here, express evidence is presented, a western blot, which demonstrates this point. The western blot is an assay in which protein mobility in a gel would be affected by glycosylation or by amino acid modification. So if the protein mobility is the same between unmodified and unglycosylated control protein and the plant expressed protein,

that is strong evidence that the protein in the plant is also unmodified and unglycosylated. In response to this evidence presented in the action, Applicant simply argues that it is insufficient. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Here, applicant's statements lack any evidentiary support while the conclusion in the office action is grounded in evidence presented in the Lee reference.

Applicant then relies upon overcoming the 102 rejection to overcome the 103 rejections. Because the 102 rejection is maintained for the reasons given above, the 103 rejections are also maintained.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

January 9, 2003